

THE SUBSTANCES CAUSING VASOCONSTRICTION

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EPINEPHRINE

THE name epinephrine was applied by Abel to the active principle which he isolated in 1897 and which was subsequently found to be a benzoyl derivative (1). This name was adopted by the American Medical Association in place of the protected name adrenaline.

The first of this group of substances was revealed by the experiments of Oliver and Schäffer (2) in 1894 with extracts of the suprarenal glands. In 1901 Aldrich and Takamine isolated the active principle and named it adrenaline. Friedmann in 1906 obtained its structural formula. It was synthesized by Stoltz and Dakin in 1905. The studies of these workers made evident that other chemically related bodies produced more or less similar actions as did those of Barger and Dale (3).

Oliver and Schäffer showed quite clearly that an extract of the suprarenal glands caused contraction of the arteries and led to an increase in the beat of the auricles and ventricles. They further showed that the effect of the active principle was peripheral upon the organs themselves and not due to an action on the central nervous system.

In the thirty-five years that have passed since the publication of their main paper, it has been established that the amount of epinephrine present normally in the blood stream is extremely small; how small we do not know. The figures of Stewart and Rogoff would suggest about 0.002 mgm. in the blood of a man, and it has been shown that its presence is not necessary to maintain the blood pressure. It may be that even this small amount has some importance in cardiac metabolism, allowing the heart to do the same amount of work with a lower consumption of oxygen, as suggested by Gremels (4), who found this to occur when from 0.0026-0.008 gamma per kgm. per min. of epinephrine was infused into a cat. In his experiments, increasing the amount three times led to an increased consumption of oxygen, but even this amount is far smaller than that which may be released in the dog by stimulation of the sciatic nerve. Cannon (5) estimates that in fright, pain and asphyxia, as much as 0.001 mgm. per kgm. body weight per minute may be released reflexly from the gland. This result is approximately what might be expected from the intravenous injection in man of 0.5 cc. epinephrine hydrochloride, when a rise in blood pressure would occur. Samson Wright (6) reports that if 1.5 cc. of the solution of epinephrine hydrochloride be injected subcutaneously in man, it will produce an increased cardiac rate with increased minute volume, but with no in-

crease in pressure, as the opposing reflexes are able to offset any vasoconstriction. The oxygen consumption will, however, increase some 20 per cent. Absorption from a subcutaneous injection of 0.5 cc. usually will not give a concentration of epinephrine adequate to overcome the controlling reflexes and frequently will produce no increase in cardiac rate, while a smaller amount administered intravenously will do so. The anesthetist is concerned with the use of epinephrine to produce a concentration either equal to what may be produced reflexly, or in some cases, somewhat larger quantities, and not with concentrations such as those that produce the usual textbook picture.

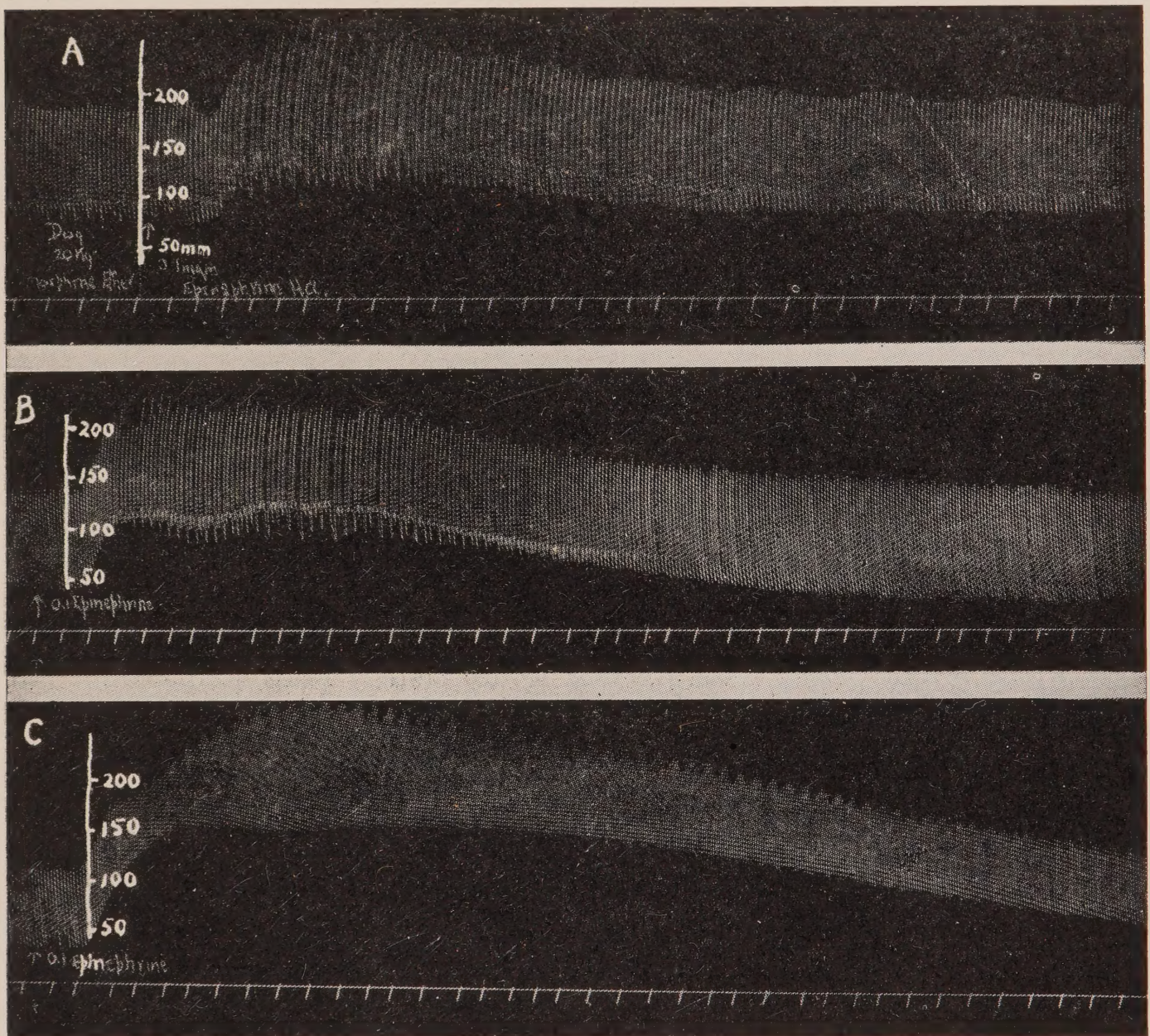
Indeed, the usual textbook picture of the abrupt rise of blood pressure from normal to 75 to 150 mm. Hg above normal, with its almost equally prompt fall, reaching the normal level in two minutes or so, conveys a totally erroneous picture of the action of epinephrine used therapeutically. In such a case the high pressure throws an undue strain upon the heart which, owing to its wasteful use of oxygen, it cannot master. The abrupt fall is in part an expression of its failure to cope with an impossible effort.

Let us consider rather the effect of a lesser dose administered by intravenous injection. The epinephrine produces a vasoconstriction in the arterioles of the skin and splanchnic area. The constriction reaches its maximum in a few seconds after reaching the vessels, and is maintained for some minutes. The rise in diastolic pressure leads to decreased cardiac emptying, decreased stroke volume and pulse pressure. The blood not ejected with the normal inflow increases the diastolic length of the fibres and leads to gradually increasing stroke volume and pulse pressure. This phase lasts again a few seconds. Then another factor intervenes; namely, an increased venous return. The spleen constricts due to the effect of the epinephrine, as do certain of the larger abdominal veins. Possibly in man, as in the dog, some blood is released from the liver. A little blood is transferred from the contracting vessels to the venous side. The increased venous inflow again stretches the ventricular fibres, and an increased stroke volume and pulse pressure results with a further rise in mean pressure. The epinephrine causes a dilation of the coronary arteries, and with the increased pressure, a much greater blood flow, with increased supply of oxygen to furnish cardiac energy. The increased pressure has enhanced the flow through the cerebral circulation and that of the muscles, and even through the constricted vessels the flow may be increasing. A more or less great increase in rate of circulation occurs so that there is increased flow through the pulmonary arteries and increased oxygen supply per minute to the body and increased venous return to the left heart, with increased minute volume and a further rise of pressure. This whole sequence of events requires perhaps a minute.

This description is again abnormal, though it may occur under certain anesthetic conditions when the centres in the medulla are de-



pressed. Usually we find in animals, and this occurs in normal man, that the initial rise in pressure in the carotid sinus and in the arch of the aorta sets into activity the pressor sensory receptors and volleys of impulses are sent via the glossopharyngeal and the vagus nerves to the cardio-inhibitor and the vasomotor centres. Their altered activity leads to a decreased cardiac rate and some vasodilation, particularly in vessels not strongly constricted by epinephrine itself. In this case, after the primary rise in pressure due to vasoconstriction, the cardiac rate decreases, diastolic pressure tends to fall, the heart has a longer



A. Dog, 20 kg., under morphine and light ether. B.P. written with a tonometer giving pulse pressure values. Mean B.P. rose from 140 mm. Hg to 175 mm. after an intravenous injection of 0.1 mgm. of Epinephrine Hydrochloride. Note the marked decrease in pulse rate due to carotid and depressor reflexes. Vasodilation undoubtedly also occurred. Pressure reached normal level again in 105 seconds. B. Now under very deep ether. B.P. lower, 85, rising to 155. Cardiac reflexes less marked. Rise lasts 140 seconds and the pulse pressure is still above normal at this time. C. High spinal anesthesia has now been added. No cardiac reflexes are apparent. B.P. rose from 72 to 215 mm. and lasted 225 seconds. In this tracing the two stages in the rise of pressure are very evident. The first is due to the vasoconstriction only and is accompanied by a decreased stroke volume and pulse pressure. Then an increased venous inflow from spleen, liver, veins and constricted vessels and the increased circulation rate occurs with increased stroke volume and pulse pressure.

interval to fill and the stroke volume is increased. Then the increased venous inflow from spleen, veins, and liver, takes effect and the stroke volume increases further. Again, the flow through the coronaries increases, as does that through the cerebral and vessels within the muscles, even though the blood pressure rises some 20–30 mm. Hg. The rate of circulation usually increases and so does the minute volume. A redistribution of the blood in circulation thus occurs. This is similar to the effect produced by pain or fright when the blood pressure may not be raised greatly, and it approximates the effects of a subcutaneous injection described by Samson Wright and referred to above. Even when in this case blood pressure has fallen to its normal level, the redistribution still exists and the complete return to normal outlasts the increase in pressure.

But the anesthetist rarely employs epinephrine when the blood pressure is normal but only when it has fallen, due to either vasodilation or cardiac failure. Let us consider the case where the fall is due to vasodilation. As before, epinephrine causes vasoconstriction, increased pressure, in a few seconds increased venous return, increased stroke and minute volume and increased rate of circulation, but as long as the mean blood pressure does not much exceed the normal, the carotid sinus and depressor reflexes of the aortic arch do not exert much effect. The decreased cardiac rate does not occur. Indeed, the rate may be increased (*a*) by the effect of epinephrine on the sinus node and (*b*) by the increased venous pressure setting up the Bainbridge reflex. In animals in such a case the rise of pressure may last eight or ten minutes.

Even more favorable conditions exist when the vasomotor and cardio-inhibitor centres are depressed by some drug. Here again the rise of blood pressure with its attendant redistribution of blood and increased circulation rate may last much longer. Indeed, a pressure slightly above normal may last for 10–15 minutes. If the original cause of the low pressure has been due to depression of the vasomotor centre caused by a drug, the increased cerebral blood supply may aid in removing the cause.

As is well known, even in the case of the decrease in pressure being due to a cardiac failure, the patient may be saved by an intracardiac injection of epinephrine. Some 0.3 cc. of the *Liquor Epinephrinae Hydrochloridi*, preferably diluted with some 25–50 cc. of saline, should be injected into the left ventricle, the object being to have some enter the coronary arteries and so reach the sinus node and the musculature. Epinephrine increases the activity of the node and increases the contractility of auricular and ventricular muscle. Not only this, but as the epinephrine reaches the coronary vessels they will dilate, and with the recovery of arterial pressure, the heart will again be supplied with blood and oxygen. It is evident from the cases reported by Asteriades (7) and others that this use of epinephrine may be effective even in the case of cardiac failure under chloroform.

Under spinal anesthesia an abrupt fall in pressure may occur. Whether one agrees with Smith, Rovenstine, et al (8), who claim that the blocking of the sympathetic fibres, which go to make up the major and minor splanchnics which supply the vasoconstrictor fibres to the viscera and of those which supply the vessels of the lower limbs, does not lead to a dilation of the vessels in these areas, or with those who claim that these vessels must dilate as they are receiving normally a tonic vasoconstrictor supply, it must be realized that the mechanisms for the maintenance of a normal blood pressure have been interfered with. Normally a fall of pressure at the carotid sinus and aortic pressure endings leads reflexly to increased cardiac rate, vasoconstriction and to release of epinephrine from the adrenals. Yet in the case of a high spinal anesthetic the sympathetic pathways to the spleen, the adrenal and to the vessels of the lower limbs and viscera are blocked. Only the increase in cardiac rate and constriction in relatively minor vascular areas are available. The normal or increased blood flow to the heart and brain which these reflexes strive to maintain cannot be accomplished. It is quite obvious that here there are indications for the use of epinephrine.

SURGICAL SHOCK

In the case of true surgical shock there is not the same justification for the use of epinephrine as in other cases of low blood pressure. Here the fall of pressure is due to the escape of fluid from the capillaries. This loss of fluid will be accompanied by a fall of pressure and this in turn will lead to reflexes from the carotid sinus and aorta resulting in vasoconstriction and secretion of epinephrine. The arterioles will be constricted. Only when the adrenal medulla was exhausted could there be an indication for the use of epinephrine, and then in very low physiological concentration which might do nothing more than improve cardiac contractility.

ETHER

When ether is administered, it is known that cardiac rate is increased, blood pressure rises, minute volume increases and the value for blood sugar increases. Hence many persons have inferred that this is due to a liberation of epinephrine. Indeed, Elliott (9), Fujii (10) and Kodama (11) and others have shown that content of epinephrine in the adrenal gland falls during an ether anesthesia. It has, however, not been proved that the increase in heart rate, the increase in blood sugar and circulation rate are entirely due to a release of epinephrine either reflexly or due to the action of the ether on the adrenals, but may be due to the action of ether elsewhere as Heymans (12) has shown that the increased heart rate may be explained on the basis that ether depresses the mechanism of the carotid sinus.

In conclusion, one should refer to the use of epinephrine with local anesthetics, where the great advantage lies in the constriction of the

minute vessels, and consequently the decreased circulation leads to a slower fall in the local anesthetic concentration and an increased duration of anesthesia. It seems a common misapprehension that the small amounts of epinephrine escaping from the area will have no effect. It is true that the concentration of epinephrine in the injection is low—1:50,000–1:100,000—but if the total injection is large some will escape. It is well known that a subcutaneous injection will relieve the itching in urticaria or an attack of asthma. Those who use it for these purposes are aware that there may be some palpitation and discomfort even if the blood pressure does not rise. The epinephrine has, in part, left the site of injection and has reached the bronchi, the skin and the heart. The reflex mechanisms, however, succeed in confining the rise of blood pressure to less than 10 mm. of mercury. It may be that the concentration of epinephrine in the blood stream has not reached a sufficient concentration to give an effective vasoconstriction, while it has been ample to dilate the abnormally constricted bronchi.

CONTRAINDICATIONS

As we have noted, epinephrine administered even in low concentration changes cardiac metabolism, and in the ordinary therapeutic dose intravenously or subcutaneously, it also produces changes in cardiac function. Levy (13) showed that in light (non-surgical) chloroform anesthesia in cats an injection of epinephrine led to sudden ventricular fibrillation and death. In dogs the effect is not so marked, as judged by the work of Meek, Hathaway and Orth (14), as in none of their animals did fibrillation occur, but in a large percentage ventricular extrasystoles, and in about 10 per cent. ventricular tachycardia of short duration, did occur. Cyclopropane, like chloroform, may cause extrasystoles, and again the above authors have shown that epinephrine caused, in dogs subjected to cyclopropane anesthesia, an even higher percentage of ventricular tachycardia and of ventricular extrasystoles. Consequently it is probably not wise to administer epinephrine to patients under cyclopropane. Against this must be set the fact, as mentioned above, that patients have been given epinephrine in cases of cardiac failure under chloroform.

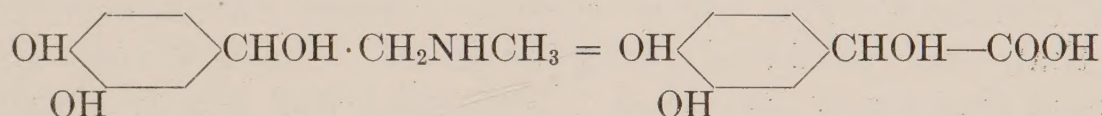
MODE OF ACTION

The work of Loewi and Cannon has made it clear that the stimulation of a sympathetic nerve leads to the liberation of an epinephrine-like substance “sympathin” and that this unites with the cell, causing its activity or depression. There is still a dispute as to whether sympathin or epinephrine is liberated and unites with the cell and also, as Cannon's school have shown, it may be carried away by the blood stream and increase the activity of other cells. Hence it seems reasonable to suppose that injected epinephrine also unites in some manner

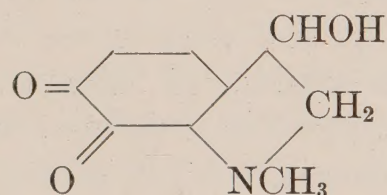
with the cells it activates or depresses. It has also been abundantly shown by Meltzer and Auer and many other workers that epinephrine produces its characteristic effect after sympathetic nerve fibres to the organ have degenerated.

Straub has proposed the theory that the action of epinephrine only occurs while it is entering the cell, and that once the internal concentration equals that externally, the action ceases. He takes it for granted that epinephrine is rapidly destroyed intracellularly. This would, in his opinion, account for two well established facts. First, that very soon after the action of any reasonable dose of epinephrine is over, another dose of the same size gives exactly the same effect. Secondly, that blood pressure can be maintained in the completely pithed animal at any desired level by a constant intravenous infusion.

The chemical structure of epinephrine makes it liable to destruction in various ways. Blaschko has isolated an enzyme, amino oxidase, which attacks a terminal amine NH_2 group and in the case of tyramine parahydroxyphenyl acetic acid is formed. Were merely the same effect produced with epinephrine,



the change, as shown above, would take place and activity would be lost (Blaschko (16) 1937). But in the body there is a much more common oxidative system, the so-called cytochrome system, and this transforms epinephrine into adrenochrome.



This requires the uptake of two atoms of oxygen with the loss of activity and the formation of a red compound (Green and Richter (17)).

Atmospheric oxidation of adrenaline leads to a loss of activity with the uptake of two atoms of oxygen. This reaction is prevented from taking place by the presence of ascorbic acid, glutathion and amino acids (18). It will not account for the loss of epinephrine in the body. Possibly the cytochrome oxidation is also interfered with by ascorbic acid.

It would seem that Blaschko's enzyme which is abundant in the liver is the most likely mode of the destruction of circulating epinephrine, but it is as yet not clear what happens to epinephrine when it becomes attached to tissues. There is no doubt, as pointed out above, that Blaschko's enzyme will destroy the activity of tyramine, epinephrine, epinine and dihydroxyphenylethylamine readily, all other members of the ethanolamine group, sympathol (meta or para), arterenol, adrena-

lone less readily, and will unite with, but will not destroy, or will destroy only extremely slowly ephedrine, corbasil, and colephrine. This is probably true of the other members of the propanolamine group (Blaschko). It seems at the present probable that some similar enzyme system destroys epinephrine after it has become attached to cardiac and vascular muscle cells.

EPHEDRINE

Although Nagai in 1887 isolated this alkaloid from *Ephedra vulgaris*, it was not until the work of Chen and Schmidt (19) that its importance became recognized. Their studies showed that ephedrine produced a rise in blood pressure, an increase in cardiac rate and contractility and raised the blood sugar. The rise in blood pressure, like that of epinephrine, is primarily due to contraction of arterioles in the skin and splanchnic area, a contraction of the spleen and veins (Mugge (20)), to which is added the increased cardiac contractility, if moderate doses are used. Of these effects, that on the vessels seems to be less marked than with epinephrine, while that on the spleen is more marked (Mugge). The whole rise of pressure lasts several times longer than that produced by epinephrine. Cardiac rate appeared to be more frequently increased. The effect was clearly shown to be peripheral, as it occurred in the completely pithed animal. Ephedrine produced, indeed, effects resembling epinephrine, but from the first, certain differences were observed. (a) The effects of ephedrine lasted longer. This we now know is due to its less rapid destruction by the liver. This also is the reason why it has relatively much more effect when given subcutaneously, and even more when given by mouth, than has epinephrine. (b) The studies of Schaumann (21), Kreitmair (22), Hildebrandt (23), and Mugge (20), showed that it produced relatively little effect on perfused vessels. (c) A second dose, administered after the effect of the first had declined, produced less effect, and succeeding doses still less (a phenomenon now termed tachyphylaxis). This is not due to an immunity, for Rühl (24) showed that rabbits injected daily for months still showed the characteristic effect. (d) Schaumann showed that in the perfused frog's vessels the vasoconstrictor effect of epinephrine was greatly increased by a previous apparently ineffective dose of ephedrine. Csepai and Doleschall (25) in 1925 showed that after ephedrine, epinephrine produced a greater effect in man. Finally, Burn (26) showed clearly that ephedrine was without arteriole effect, save when circulating epinephrine was present. Meantime, Blaschko's enzyme had been studied, and as it has been shown that this enzyme united with ephedrine but did not destroy it, Gaddum (28) has urged the theory that ephedrine, by poisoning this enzyme (as eserine does the choline esterase), leads to circulating epinephrine (or sympathin), being adequate to produce the vascular contraction which in turn produces the rise in pressure. Gaddum then explains the tachyphylaxis by

ephedrine uniting with the vascular cells, but without obvious effect. The cell receptors with which the ephedrine unites are, Gaddum assumes, those with which epinephrine also combines, and hence the lessened effect of repeated doses, as less epinephrine can unite with the cell. Gaddum and Kwiatkowski (27) showed that even with the isolated perfused rabbit's ear, ephedrine, while it alone produced no vasoconstriction, greatly increased the effect of subsequent doses of epinephrine, as the presence of ephedrine prevented the destruction of the epinephrine. They further showed that sympathetic stimulation of the vessels of the perfused ear led to a larger amount of sympathin or epinephrine being liberated into the perfusing solution than occurred previous to its administration. Unfortunately, Richter and Tingey (29) have shown that epinephrine, in the concentration prevailing in Gaddum's experiments, is very slowly destroyed by Blaschko's enzyme, and that ephedrine in the concentrations present in Gaddum's experiments did not inhibit the enzyme. They further failed to find any enzyme in the macerate from the rabbit's ear. They also point out that the chief source of this enzyme is the liver.

The total evidence, however, does suggest that ephedrine depresses whatever enzyme system normally destroys epinephrine, though this may not be Blaschko's enzyme.

The other explanation of subsequent doses of ephedrine not producing the full rise of pressure produced by the first, raises a more serious point in the action of ephedrine. This explanation depends upon experiments which appear to show that ephedrine has a deleterious effect upon the heart. Both theories have in common the assumption that ephedrine, after union with the cell, is very slowly destroyed or removed. This assumption seems justified by such work as that of Kreitmair, who showed that after a single moderate dose of epinephrine, the effect of a given dose of epinephrine was increased for two hours or more. The evidence of cardiac damage was inferred by Schaumann, and is strongly stressed by Hildebrandt and by Mugge. The experiments of these two workers showed that a first moderate dose of ephedrine increased the cardiac contractility slightly and increased the coronary flow, while repetitions of such injections led to a definite decrease in coronary flow and progressive cardiac failure, probably in part dependent on the decreased flow. Larger doses of ephedrine led from the first to cardiac dilation.

Further, we have evidence of some direct cardiac effect of ephedrine in the work of Meek and Seevers (30), who refer to other less thorough studies of the same kind. These authors studied the effect of doses of ephedrine from 0.5–20 mgm. per kilogram (1 milligram per kilogram would correspond approximately to the dose given before spinal anesthesia in man). In all dogs but one there was an initial bradycardia with doses of 1–20 mgm. This is doubtless due to a carotid sinus reflex. This reflex may lead also to extrasystoles and slow ectopic rhythms.

But ephedrine also stimulated the lower automatic centers and, if this effect is marked, extrasystoles or tachycardia may occur.

In these papers there is evidence that there is an optimal favorable initial dose of ephedrine and of the accumulation of repeated small doses until an optimal effect is obtained. The evidence may then be drawn together as follows: Ephedrine has little effect upon vessels and the effect it apparently produces is due to circulating epinephrine. This causes the primary coronary dilation, the constriction of the spleen which, according to Mugge, outlasts the constriction of the arterioles, and of the veins which is even longer-lasting, but the union of the ephedrine with the cells of these structures prevents or decreases the entrance of epinephrine when present in merely the normal circulating concentrations, but will not prevent higher concentrations, as obtained by injection, having an even increased effect, until the amount of ephedrine is such that epinephrine causes vasodilation or cardiac failure, and either owing to a direct effect of ephedrine on the coronary vessels or on the heart muscles, decreases cardiac contractility.

EPHEDRINE IN MAN

Chen and Schmidt found that 40–60 mgm. intramuscularly produced rises in blood pressure of 20–30 mm. Hg, with a decreased heart rate, while 60 mgm. per os produced a rise in one case from 128/60 to 150/68, with a decrease in pulse rate from 74 to 60. The effect began in about 30 minutes and lasted for two hours.

Foged (31) found that doses per os of 1.4–2.0 mgm. per kilogram (i.e. from 84–120 mgm. for 182 lb. man) produced rises of pressure of from 10–35 mm. Hg in different cases. The maximal rise occurred in 30–90 minutes. Intravenously 1.3–2.0 mgm. per kgm. produced rises in various cases of 30–60 mm., the maximal effect occurring in 20–60 minutes with a gradual decline for 2–3 hours. Similar results are reported by Oremus.

Csepai and Doleschall found again that 10 mgm. of ephedrine intravenously produced rises in blood pressure 10, 12 and 35 mm., while 0.01 mgm. of ephedrine intravenously produced a 10, 15 or 35 mm. before ephedrine; after ephedrine the same amount produced increases of 22, 40 and 95 mm.

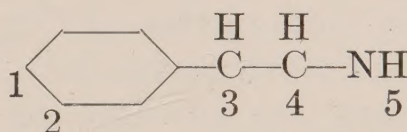
The larger doses lead to a decrease in anesthesia and the production of restlessness, tremor, perspiration, warmth or chilliness and gastric distress.

From the above evidence certain important conclusions may be fairly drawn. If ephedrine has been given in an adequate dose of 50–100 mgm. its effects will last for an hour and a half or two hours, at least. Epinephrine given during this time will have more than its usual effect and the effect will last longer. Further, the effectiveness of ephedrine depends on circulating epinephrine and if the circulating amount of this hormone be less than normal or even absent, as it well might be if

the innervation of the adrenals had long been blocked, epinephrine should be given with or before ephedrine. Even a subcutaneous injection of epinephrine, which normally would produce no effect, would be adequate to make ephedrine effective. But all in all it is evident that epinephrine is a more valuable agent than ephedrine, though the latter may be used to prolong the effect of the former, and for this purpose quite small doses of ephedrine, 25–50 mgm., are probably adequate.

OTHER MEMBERS OF THIS GROUP

It will save a great deal of repetition if the differences in the structures of the epinephrine and ephedrine molecules are understood. The first difference lies in the absence of the two hydroxyl (OH) groups on the phenol ring in ephedrine. This probably contributes to its stability. The second lies in the fact that there are three carbon atoms in the chain preceding the NH_2 group. In other words, the side chain in ephedrine is a propanolamine one, while in epinephrine it is an ethanolamine. We can, indeed, divide the members of this general group into these two classes and the structure of those that will be discussed is shown schematically in the following Table.



Numbers of Places Substituted.....	1	2	3	4	5
Epinephrine. Adrenaline.....	OH	OH	OH	H	CH_3
Sympathol. Synephrine.....	OH	H	OH	H	CH_3
Meta Sympathol. Neosynephrine.					
Adrianol.....	H	OH	OH	H	CH_3
Epinine.....	OH	OH	H	H	CH_3
Arterenol. Noradrenaline.....	OH	OH	OH	H	H
Ephedrine.....	H	H	OH	CH_3	CH_3
Corbasil. Cobefrin desoxy-norephe-					
drine.....	OH	OH	OH	NH_2	CH_3^*
Veritol.....	OH	H	H	CH_3	CH_3
Suprifene.....	OH	H	OH	CH_3	CH_3

* Replaces the NH_2 group.

It should be remembered that the occurrence of two hydroxyls in the phenyl ring, as in epinephrine, epinine and arterenol, lead to a more rapid destruction and a less sustained action; that the presence of only one hydroxyl decreases the potency but lengthens the action.

Further, the members of the propanolamine group are not appreciably destroyed by Blaschko's enzyme and have a more prolonged but weaker action. In sufficiently large doses they would be expected to show tachyphylaxis, but not all members do so as is mentioned below. They will all potentiate the effect of epinephrine.

SYNEPHRINE. SYMPATHOL

This epinephrine-like substance, as many of the others, was studied first by Barger and Dale (3). Given intravenously it produces a prompt rise of blood pressure, but a dose some 50 times larger than that of epinephrine is required. The pressure remains elevated for a longer time—20 minutes. The rise is due to an increased venous return from the spleen and liver, and to some vasoconstriction of arterioles in skin and muscle and probably veins (Hochrein and Keller (33)). The coronaries are dilated (Ruhl (34)) but apparently less so than with epinephrine (Gremels (35)) and cardiac irregularities are not so readily produced as with the latter. The effect of synephrine on heart rate is much less than with epinephrine (Tainter and Seidenfeld (36)) but cardiac contractility is improved. While according to Ruhl epinephrine clinically is of most value in improving cardiac activity, synephrine is also of value and according to Gremels may be of more value as it does not increase the oxygen requirement of the heart so much. Synephrine is more stable in solution than is epinephrine (Ehrismann and Maloff (37)). It constricts perfused vessels (Tainter and Seidenfeld) and repeated injections produce equal effects. Hyperglycemia is far less than that produced by epinephrine (Pflug and Brentano and Pflug (38)). Ruhl states that the most useful dose for man is 100–150 mgm. intramuscularly. It is much less effective per os. In emergency such a dose may be given intravenously.

NEOSYNEPHRINE. META-SYMPATHOL. ADRIANOL

The study of metasymphathol has shown that it has only about 1/15 of the effectiveness of epinephrine in raising blood pressure when given intravenously, but its action lasts longer and it is not so apt, when producing a moderate rise of pressure 30–40 mm. Hg, to produce extrasystoles or manifest a deleterious cardiac effect. Subsequent doses do not exhibit a decrease in its effectiveness (Kuschinsky and Overdisse (39), and Johnston (40)). As is to be expected, it shows little evidence of central action, and patients do not show the restlessness, tremor or decrease in anesthetic depth that may occur with ephedrine (Brunner and de Takats (41), and Johnston). The rise of blood pressure produced by subcutaneous or intramuscular injection appears in doses of 5 mgm. to be about 30 mm. Hg, but varies greatly from 0–70 mm. The pulse rate is usually decreased, e.g. 102 out of 114 cases (Lorhan and Lalich (42)). In some there may be an increase. The rise of pressure after intramuscular injection begins in about 4 minutes, lasts about 45 (Tainter and Stockton (43)). About 5 mgm. subcutaneously or intramuscularly per patient may be considered a usual prophylactic dose in spinal anesthesia (Bittrich (44), Johnston, Brunner and de Takats, Lorhan and Lalich). In some cases irregular hearts become more regular and this is compatible with the observations of Kuschinsky and

Overdisse, that neosynephrine has less deleterious effect than epinephrine. It seems from their work and that of Gremels that synephrine is even more likely to improve cardiac action. It must be remembered that overdoses may produce some deleterious effect on cardiac action (Charlier (45)). This drug has, therefore, certain advantages over epinephrine, namely it is less likely to produce cardiac irregularity of a serious type (i.e. those not due to reflex bradycardia or nodal rhythm but due to a stimulation of subordinate pacemakers). It does not decrease the effect of premedication, but on the other hand it does not produce the prolonged effect of ephedrine.

Epinine has apparently been very little studied. Its action seems to resemble closely that of epinephrine but is not more than one-seventh as potent but its effects last a little longer (Barger and Dale). It is destroyed by Blaschko's enzyme.

ARTERENOL

This substance is the only member of the series which is more active than epinephrine (50 to 35, Barger and Dale; 50 to 40, Tainter (46)) and its effect lasts a little longer.

VERITOL

Veritol has been subjected to a great deal of study in Germany and has been used in connection with spinal anesthesia, both prophylactically as ephedrine is given and during a fall of blood pressure (Kreise, Garan et al (47)), but these authors found it of no value in severe circulatory collapse. As pointed out above it produces a prompt, long-lasting rise in pressure. It is more potent than synephrine but its effect does not last quite as long as ephedrine (Grosse-Brockhoff and Kaldenberg (48)). The effects on blood pressure occur in the fully pithed animal (Eichler (52) and Lindner (51)). In animals an examination of its action has shown that an increased venous inflow due to the contraction of the spleen (Rein (49)) and from skin and muscles (Zipf (50)) is the first cause of the rise of pressure; to this is added a less marked vasoconstriction elsewhere. Its effect on perfused vessels, like ephedrine, is slight or absent (Lindner). The cardiac contractility seems to be improved. When the heart has been poisoned, veritol distinctly improves its action (Rein, Zipf and others). If large doses are used, a second one has less effect. This is in part due to the contraction of the spleen persisting after blood pressure has fallen to normal; in part due, doubtless, to the reasons advanced in the case of ephedrine. Coronary flow is increased but not as much as with epinephrine. Oxygen consumption for the work done by the heart is decreased by small (Rein), not by large doses.

These effects have been confirmed in man (Sturm and Voges (53)) with 10 mgm. doses intramuscularly. Such a dose produced no un-

toward symptoms, while 20 mgm. caused vomiting, headache, dizziness, cold feet and hands. Other authors noted extrasystoles, Parade (54) with 4 mgm. and Köhler (55) with 20 mgm. in some cases. With higher doses they apparently occur more frequently (Aschenbrenner and Cudas-Thompson (56)). It has little effect per os unless large doses, 60 mgm., are used (Reindell, Baurhenn, and Braunbehrens (57)). Ten mgm. subcutaneously or intramuscularly will increase the systolic blood pressure from 20–70 mm. Hg in 30–40 minutes (Sturm and Voges; Robbins and Ginader (58)). Diastolic pressure rises less (Köhler). The rise varies greatly with the individual. The effect lasts 30–40 minutes or even 70. Heart rate is usually reduced (pressor reflex) but in certain cases increased.

Veritol has little effect on blood sugar (Zipf). In susceptible patients such doses, or larger ones, produce other symptoms, such as pounding heart, sweating, and nausea, and may have some effect cerebrally, e.g. restlessness. Stumpf (49) presents some evidence that depth of anesthesia may be decreased.

SUPRIFINE, PARA-OXY-EPHEDRINE

Like ephedrine this substance has no effect on perfused vessels in the absence of epinephrine, but potentiates the latter's effect. It raises the blood pressure more rapidly than ephedrine and higher but shows less tachyphylaxis (Schaumann (61)). It has apparently a greater effect on the heart than on the vessels and is less toxic than ephedrine (Sturm and Stuckmann (60)). It produces, like ephedrine, no great change in the blood sugar level. A dose of 5 mgm., according to Oremus (32), increases the cardiac minute volume greatly without much, 5–10 mgm., rise in blood pressure and the effect may last for 45 minutes.

COBEFRINE. CORBASIL

This differs from the other ephedrine-like propanolamines in that the amine does not occur on the terminal carbon but on the middle one of the side-chain and is a direct isomer of epinephrine. It is about 1/2 (Schaumann) or 1/3 as potent as epinephrine (Tainter and Thronson (62)) but its effect lasts slightly longer and is prompt in onset. According to Tainter (46) it does not show tachyphylaxis and increases the effect of epinephrine moderately. It seems to have less effect on the vessels, but more effect on the heart (Schaumann 1931), though in Tainter's animal experiments the heart rate increased only 20 per cent. for an increase of blood pressure of 20–70 per cent.

CONCLUSIONS

1. One may therefore be permitted to draw certain conclusions. Ephedrine is of value in preventing a fall of blood pressure or in combating it if circulating epinephrine is available. If not, it should be

used with small doses of epinephrine subcutaneously, or in a great emergency intravenously. An endeavor should be made to estimate the dosage of both drugs so that blood pressure will not rise greatly, if at all, above normal levels. It is evident that synephrine might well be used in place of epinephrine as it does not increase the oxygen consumption of the heart so greatly and its action is potentiated by ephedrine, and this is substantiated by the work of Cranston and Bieter (63). Neosynephrine, though the rise of pressure it produces is somewhat longer, has less of the beneficial cardiac effect than synephrine. Further, there seems good reasons for the use of veritol in place of ephedrine, as its cardiac action is more favorable.

Finally, the differences between these substitutes is not so great that it would be wise for any anesthetist to learn to use one of the propanolamine group and one of the ethanolamine group wisely and skillfully rather than to experiment with a larger number. There are other members of both groups which have not been referred to at all, and which will doubtless be marketed and their claims pressed, but the anesthetist should not take them up without suspicion.

EPINEPHRINE SUBSTITUTES WITH LOCAL ANESTHETICS

2. It has recently been suggested that some of the epinephrine substitutes should be used in place of epinephrine with local anesthetic solutions. For this purpose it must be remembered that with the exception of arterienol they are all less effective than epinephrine. There does not seem any adequate reason for the employment of any of the ephedrine, propanolamine group particularly in view of the work of Tainter and Throndson (62), who have shown that the combination of cobefrine with procaine was definitely more toxic than of procaine with epinephrine. The combination of procaine with synephrine or neosynephrine would seem more reasonable and it may prove that the undesirable tachycardia might be lessened. This has been confirmed for neosynephrine (Tainter and Throndson).

POST PITUITARY EXTRACT

The vasoconstrictor actions of post pituitary extract were described by Oliver and Schäffer in 1895. The active principle was finally separated into two fractions by Kamm and Aldous. As is well known, the subcutaneous or intramuscular injection of 1 cc. of pituitary extract or of equivalent amounts of the pressor principle do not produce much rise in blood pressure in normal human beings; often there is no rise in systolic pressure and it rarely amounts to 15 mm. Hg. Diastolic pressure rises perhaps a little more but not often above 10 mm. The rise is slow in development and lasts 45 minutes (Schmidt (64)). The pulse rate is usually decreased. The regulating reflexes are adequate to prevent much pressure rise even though there is widespread vasocon-

striction in arterioles and capillaries. Unfortunately the coronary arteries are also constricted (Morawitz and Zahn (65)) and an endeavor to force the blood pressure up significantly usually leads to such a coronary constriction that the heart fails to cope with the strain imposed on it. A complete analysis of the effects of the pressor principle on the factors involved in the blood pressure changes such as has been made for epinephrine, etc., has not been carried out. Its usefulness is, however, greatly limited by the effect on the coronary arteries and even moderate doses may cause occasional severe cardiac embarrassment in man as it does, at times, in animals.

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